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Original Article

Estimating numbers of persons with persistent hepatitis B virus infection transmitted vertically and horizontally in the birth cohort during 1950–1985 in Japan

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Aim: We estimated numbers of persons, born between 1950 and 1985 in Japan, who were persistently infected with hepatitis B virus (HBV) through vertical and horizontal infections.

Methods: HBV carrier rates with vertical and horizontal infections were computed using sex- and age-specific prevalence rates of hepatitis B surface antigen (HBsAg) and hepatitis B e-antigen (HBeAg) by mathematical model. Probabilities of vertical HBV transmission in babies born to carrier mothers with and without HBeAg were presumed to be 90% and 10%, respectively.

Results: HBV carrier rates with vertical infection stayed contrast at approximately 0.3% in birth cohorts through 36 years (1950–1985), both in men and women. By a remarkable constant, HBV carrier rates with horizontal infection decreased steadily from 1.43% to 0.10% in men and from 0.95% to 0.03% in women. The estimated total number of HBV carriers born between 1950 and 1985 was 522 500 (355 488–693 606). Of them, the numbers of HBV carriers with vertical and horizontal infections were 197 574 (149 505–288 709) and 324 926 (205 983–404 896); they accounted for 37.81% and 62.19%, respectively, with a ratio of 1:1.64. The ratio between vertical and horizontal infections was 1:2.20 in men and 1:1.06 in women.

Conclusion: Vertical HBV infection had stayed constant until immunoprophylaxis of mother-to-baby transmission was implemented in 1986 in Japan. In contrast, horizontal HBV infection decreased over years. The decrease would be due to many factors, including improved socioeconomic environments, advanced medical maneuvers and equipment, and careful vaccination procedures.

Key words: hepatitis B e-antigen, hepatitis B virus carrier, horizontal infection, newborns, vertical infection

INTRODUCTION

THERE ARE AN estimated 350 million people infected persistently with hepatitis B virus (HBV) in the world.[1] Of them, the majority (75%) are living in Asia, and approximately 25% die of serious long-term complications of HBV infections, such as decompensated cirrhosis and hepatocellular carcinoma (HCC).[2] Persistent HBV infection is mainly established by vertical transmission from carrier mothers or horizontal transmission during their infancy. It is clinically and epidemiologically relevant to examine numbers of HBV carriers with vertical and horizontal transmissions, and the ratio between them, because different strategies are required to prevent each of them.

Hepatitis B e-antigen (HBeAg) in the serum of carrier mothers is a useful marker for a high possibility of vertical transmission. Persistent HBV infection is established in 90% of babies born to carrier mothers with HBeAg,[3–6] while only in 10% of babies born to those without HBeAg.[7] Thus, it is possible to estimate the number of vertical HBV infection in babies born to a given cohort of mothers in whom prevalence rates of hepatitis B surface antigen (HBsAg) and HBeAg are known.

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Vertical HBV transmission can be prevented by passive and active immunoprophylaxis of babies born to carrier mothers with hepatitis B immunoglobulin and vaccine. Since 1986, the national immunoprophylaxis program was implemented in babies born to HBeAg positive carrier mothers in Japan. It is efficient in preventing mother-to-baby transmission, except in babies who have been infected with HBV *in utero*.[8]

In this study, numbers of vertical and horizontal HBV infection were estimated for men and women who were born during the 36 years between 1950 and 1985, before immunoprophylaxis was started in Japan.

METHODS

Study cohorts

FROM THE VITAL Statistics of Japan,[9] the following data were obtained for the Japanese born during 1950–1985: (i) the number of births by sex; (ii) the number of deliveries by mothers in 5-year age groups; (iii) sex ratio of newborns; and (iv) the mortality rate. From the census in Japan, the number of subpopulation stratified by sex and age at 2005 was obtained.[10]

HBV markers in study cohorts

Hepatitis B surface antigen positive rates stratified by sex and birth year were obtained for the first-time blood donors during 1995–2000 in Japan,[11] and from the fact sheet on HBV by the National Institute of Infectious Diseases.[7] HBeAg positive rates among HBsAg positive women grouped by 10 years were reported by Sasaki *et al*.[12] The study design conformed to the 1975 Declaration of Helsinki.

Assumptions

We assumed that age-specific HBV carrier rates in mothers who were born before 1930 to be the same as those in the birth group from 1931 to 1935, which is the oldest birth group among studied subjects.[11] The possibility of HBV transmission to her baby was assumed to be 90% for a carrier mother with HBeAg, and 10% for a carrier mother without HBeAg.[7]

Estimation

Estimation of the numbers of HBV carriers with vertical infection in birth groups notched by 1 year from 1950 to 1985

1 The number of babies born to HBV carrier mothers in 1-year notched birth year j (j = 1950, 51, 52, . . . , 85:36 points) was estimated by the equation: $\Sigma_i (N_{ji} * S_{ji})$: numbers of births to mothers in the age group "i", N_{ji} (i = 1 for 15–19 years old [y.o.], i = 2 for 20–24 y.o., . . . , i = 7 for 45–49 y.o.) (Fig. 1) and HBV carrier rate in the corresponding age group of mothers, S_{ji} (i = 1 for birth in [j − 19] − [j − 15], i = 2 for birth in [j − 24] − [j − 20], . . . , i = 7 for birth in [j − 49] − [j − 45]).
2 The numbers of babies whose mothers were positive and negative for HBeAg were estimated using a group-specific HBeAg positive rate E_i (Fig. 1), and HBeAg negative rate, $1 - E_i$, by the respective equations: $\Sigma_i N_{ji} * S_{ji} * E_i$ and $\Sigma_i N_{ji} * S_{ji} * (1 - E_i)$.
3 The number of HBV carrier babies with vertical infection (CV_j) was estimated by the formula: $CV_j = 0.1 * \Sigma_i N_{ji} * S_{ji} * (1 - E_i) + 0.9 * \Sigma_i N_{ji} * S_{ji} * E_i$.
4 Using the sex ratio (G_j), the numbers of HBV carriers with vertical infection (CV^M_j) for men and (CV^F_j) for women were calculated in birth groups notched by 1 year, by the respective equations: $CV^M_j = G_j / (1 + G_j) * CV_j$ and $CV^F_j = 1 / (1 + G_j) * CV_j$.
5 Finally, rates of HBV carriers with vertical infection in men (BS^MV_j) and women (BS^FV_j), respectively, to total number of birth in men (N^M_j) and women (N^F_j) were estimated in birth groups notched by 1 year by respective equations: $(BS^MV_j) = CV^M_j / N^M_j$ and $(BS^FV_j) = CV^F_j / N^F_j$ with 95% confidence interval (CI).

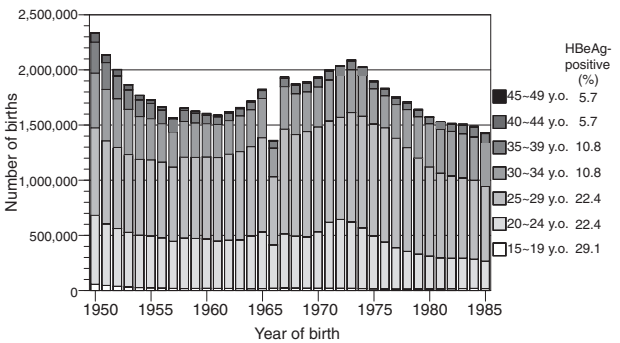

Figure 1 Number of births from mothers in 5-year age groups shifting during 1950–1985. Each component in bar graphs indicates number of live births stratified by the age of mother (15–19, 20–24, . . . , 45–49 years old). Age-specific hepatitis B e-antigen positive rates among hepatitis B virus carrier women are shown on the right.

Estimation of the number of HBV carriers with horizontal infection in birth groups notched by 1 year from 1950 to 1985

At first, number of HBV carriers was calculated by multiplying the number of births (N^{M}_{j} and N^{F}_{j}) by the HBV carrier rate in men and women in 1-year notched birth year j (33 points; 1950–1982), which were calculated by the 5-year moving average method, and that in birth year j (3 points; 1983–1985) was assumed as the same as that in the birth year cohort of 1982. The number of HBV carriers with horizontal infection (CH^{M}_{j} and CH^{F}_{j}) was calculated by subtracting the estimated number of HBV carriers with vertical infection (CV^{M}_{j} and CV^{F}_{j}) from the estimated total number of HBV carriers.

Estimation of the number of HBV carriers taking into account the mortality rate at 2005

Multiplying the numbers of HBV carriers in 1-year notched birth groups by the corresponding sex- and age-specific survival rates at 2005, the numbers of HBV carriers presumed to be alive at 2005 were obtained. They were summed to estimate the total numbers of HBV carriers.

Statistical analysis

We constructed 95% CI for the rate of HBV carriers with vertical infection using 95% CI for production of two positive rates (see Appendix for details). The χ^2-test was used for comparison of HBV carrier rates with vertical and horizontal infections. A *P*-value less than 0.05 was considered to indicate statistical significance.

RESULTS

HBV carrier rates and proportions of vertical and horizontal transmissions during 1950–1985

FIGURE 2 ILLUSTRATES HBV carrier rates in men and women born between 1950 and 1985 in Japan. HBV carrier rates decreased gradually both in men and women during these years, from 1.75% to 0.30% and from 1.27% to 0.23%, respectively.

Contribution of vertical or horizontal infection to carrier rates was estimated by a mathematical model described in Methods. The rate of HBV carriers with vertical infection stayed constant at approximately 0.3% in birth cohorts between 1950 and 1980, and decreased to 0.20% in the birth cohort of 1985. By a remarkable contrast, the rate of HBV carriers with horizontal infection decreased gradually between 1950 and 1985 both in men and women, from 1.43% to 0.10% and from 0.95% to 0.03%, respectively. The extent of decrease, in the rate of HBV carriers with horizontal infection, was higher for men than women (1.33% vs 0.92%, $P < 0.001$). The difference in HBV carrier rate with horizontal infection between men and women was statistically significant in groups born before 1972 ($P < 0.05$).

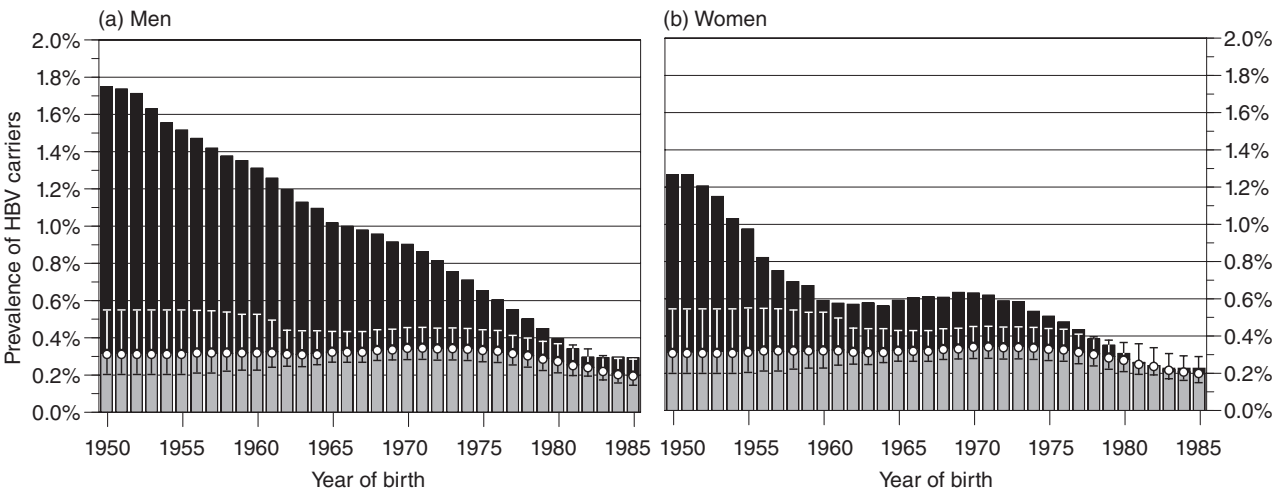

Figure 2 Hepatitis B virus (HBV) carrier rates and proportions of vertical and horizontal transmissions in yearly birth groups during 1950–1985. HBV carrier rates of vertical and horizontal transmissions are shown. Bars indicate the 95% confidence interval of vertical transmission rate. (a) Men, (b) women. ■, horizontal transmission; □, vertical transmission.

Estimation of the numbers of HBV carriers with vertical and horizontal infections in birth groups notched by 1 year between 1950 and 1985

Estimated numbers of HBV carriers with vertical and horizontal transmissions in 1-year notched birth cohorts during the 36 years between 1950 and 1985 are illustrated in Figure 3, both for men and women. The results are summarized in Table 1.

The estimated total number of HBV carriers born between 1950 and 1985 was 522 500. Of them, the estimated number of HBV carriers with vertical infection was 197 574, and those with horizontal infection was

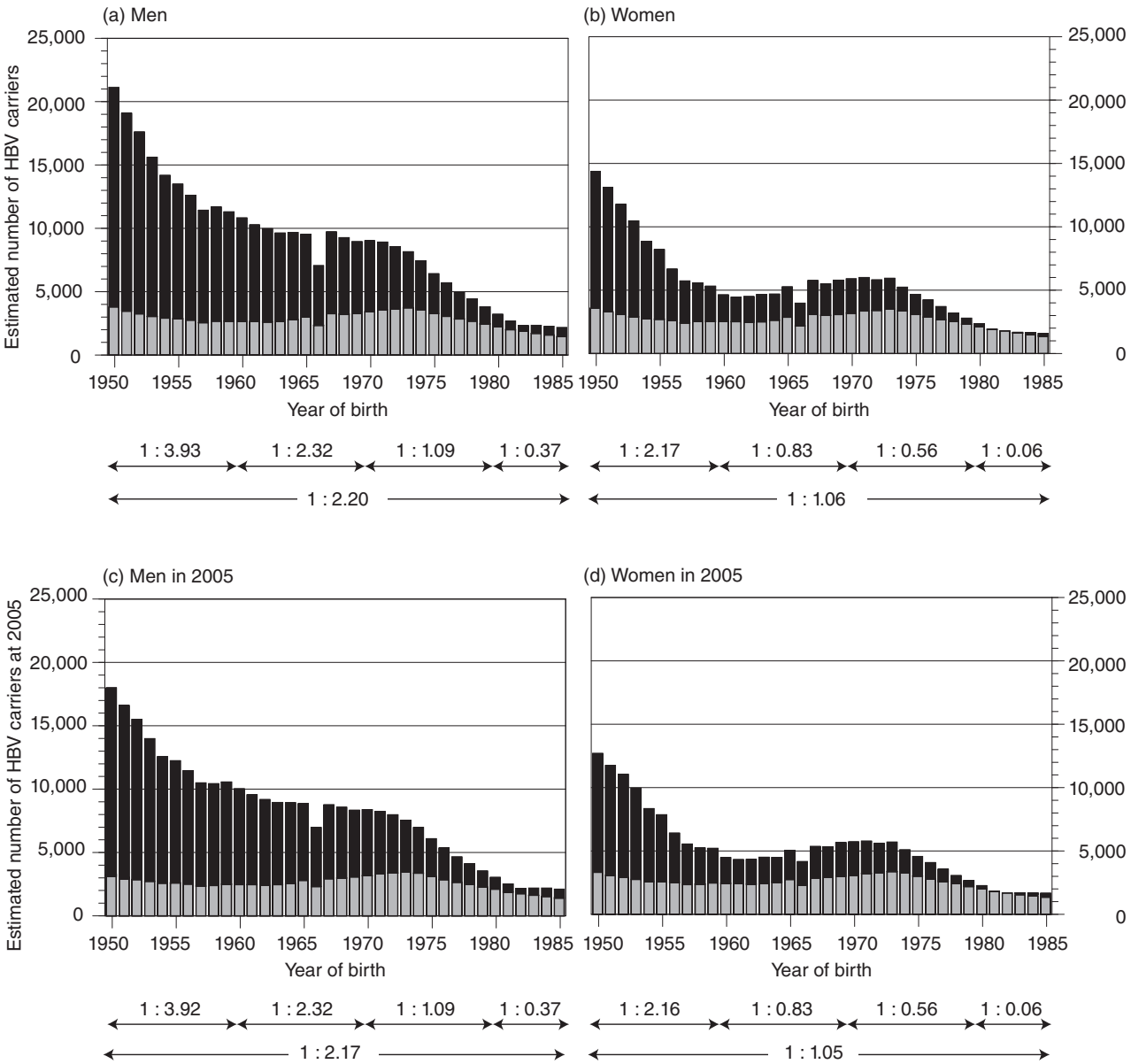

Figure 3 Estimated numbers of hepatitis B virus (HBV) carriers with vertical or horizontal transmission who were born during the 36 years between 1950 and 1985 and alive in 2005 in yearly birth groups. The ratio of the number of HBV carriers between vertical and horizontal transmissions are shown below for indicated time periods. (a) Men, (b) women, (c) men in 2005, (d) women in 2005. ■, horizontal transmission; □, vertical transmission.

Table 1 Estimated numbers of hepatitis B virus carriers with vertical or horizontal transmission who were born during the 36 years between 1950 and 1985 and alive in 2005

	Estimated number of HBV carriers (95% confidence interval)		
	Total	With vertical transmission	With horizontal transmission
Whole			
Total	522 500 (355 488–693 606)	197 574 (149 505–288 709)	324 926 (205 983–404 896)
Men	324 945 (235 765–414 592)	101 673 (76 948–148 542)	223 273 (158 817–266 047)
Women	197 555 (119 723–279 014)	95 901 (72 557–140 167)	101 654 (47 166–138 847)
In 2005			
Total	486 038 (329 981–646 011)	185 871 (140 826–271 096)	300 168 (189 155–374 914)
Men	297 031 (215 484–379 016)	93 773 (71 094–136 631)	203 258 (144 390–242 385)
Women	189 007 (114 497–266 995)	92 098 (69 732–134 465)	96 909 (44 765–132 529)

324 926; they accounted for 37.81% and 62.19% of total carriers, respectively, with a ratio of 1:1.64. Of 324 945 HBV carrier men, 101 673 had vertical infection and 223 273 had horizontal infection, accounting for 31.29% and 68.71%, respectively, with a ratio of 1:2.20.

Likewise, of 197 555 HBV carrier women, 95 901 had vertical infection and 101 654 had horizontal infection; they accounted for 48.54% and 51.46%, respectively, with a ratio of 1:1.06.

Moreover, the ratio between the number of HBV carriers with vertical infection and those with horizontal infection increased remarkably in men from 1:3.93 in the birth cohort during 1950–1959 to 1:2.32 during 1960–1969 and to 1:1.09 during 1970–1979, and reached the highest at 1:0.37 during 1980–1985. Similarly, in women, the ratio between the number of HBV carriers with vertical infection and those with horizontal infection increased steadily with 1:2.17, 1:0.83, 1:0.56 and 1:0.06 in birth cohorts during 1950–1959, 1960–1969, 1970–1979 and 1980–1985, respectively. However, during 1950–1985, while the number of HBV carriers with vertical infection decreased slightly, the number of HBV carriers with horizontal infection declined remarkably, both for men and women.

In women, the number of horizontal transmissions increased slightly during 1963–1973. This was, however, not the case for men in whom horizontal transmission decreased steadily through the study period (1950–1985).

Estimation of the number of HBV carriers taking into account the mortality rate at 2005

The number of live HBV carriers of a given birth year was calculated, taking into account the corresponding mortality rate at 2005 for the birth groups of 1950–1985 (Fig. 3). The estimated number of HBV carriers born between 1950 and 1985 and alive in 2005 is 486 038, corresponding to 93.02% of the 522 500 carriers who were born during the 36 years. Of them, the estimated number of HBV carriers with vertical infection is 185 871 (38.24%) and those with horizontal infection is 300 168 (61.76%), with a ratio of 1:1.61 (Table 1). Of 297 031 HBV carrier men, 93 773 (31.57%) had vertical transmission, and 203 258 (68.43%) had horizontal infection, with a ratio of 1:2.17. Likewise, of 189 007 HBV carrier women, 92 098 (48.73%) had vertical infection, and 96 909 (51.27%) had horizontal infection, with a ratio of 1:1.05.

In addition, the ratio between the number of HBV carriers alive in 2005 with vertical infection and those with horizontal infection in men also increased considerably from 1:3.92 in the birth cohort during 1950–1959 to 1:2.32 in 1960–1969, then to 1:1.09 in 1970–1979 and peaked at 1:0.37 in 1980–1985. Likewise for women, in birth cohorts during 1950–1959, 1960–1969, 1970–1979 and 1980–1985, the ratio between the number of HBV carriers alive in 2005 with vertical infection and those with horizontal infection was 1:2.16, 1:0.83, 1:0.56 and 1:0.06, respectively, showing an increasing trend between 1950 and 1985. As a whole, through the 36-year period, the number of HBV carriers alive in 2005 with horizontal infection decreased to an extent higher than those with vertical infection.

Thus, 93.02% of HBV carriers born during 1950–1985 would be alive in 2005. In the total of 486 038 carriers living in 2005, there were 297 031 (61.11%) men and 189 007 (38.89%) women with a ratio of 1.57:1 (Table 1). Overall, horizontal transmission was approximately sesquialteral as frequent as vertical transmission among HBV carriers. Proportion of horizontal

transmission was higher in men than women who carried HBV (68.43% vs 51.27% [1.33:1], $P < 0.001$).

DISCUSSION

PERSISTENT HBV INFECTION in a given community had been maintained by two principal routes. One of them is the vertical infection from mothers who carry HBV to their babies, and the other is the horizontal infection, typically during an early childhood.[13–15] The contribution of vertical or horizontal transmission to establish HBV carrier state is subject to host and viral factors, and varies among different countries. In Asian countries where HBV is endemic, with the prevalence of HBsAg of 8% or higher,[16] the vertical infection had been the main route of transmission for establishing HBV carrier state.

In 1980, plasma-derived hepatitis B (HB) vaccine was produced and introduced to babies born to mothers infected with HBV. As the HB vaccine was very efficient in preventing vertical infection,[17] the World Health Organization recommended universal vaccination of all babies, regardless of the mother's infection with HBV. By the end of 2011, the HB vaccine was introduced to 179 (93%) of the 193 member states; 93 (52%) recommended the first dose within 24 h of birth to prevent vertical transmission of HBV.[18] Hence, the contribution of vertical transmission to establish persistent HBV infection, in comparison with that of horizontal transmission, has to be examined in persons born before the implementation of HB vaccine to prophylaxis of vertical transmission.

Japan is a country of low endemicity for HBV, with the prevalence of HBsAg of less than 2% at the same level as those in Australia and New Zealand, although they belong to Asia.[16] Because the vertical infection was regarded as the principal route for establishing persistent HBV carrier state, a national program for passive and active immunoprophylaxis of babies born to carrier mothers was launched in 1986.[8] Initially, only the babies born to carrier mothers with HBeAg were indicated to immunoprophylaxis, in view of a high efficacy (~90%) of transmitting persistent HBV infection to their babies.[3–7,19] Since 1995, the indication was expanded to include babies born to carrier mothers without HBeAg.

In this study, we estimated the contribution of vertical and horizontal transmissions to the HBV carrier state in Japan. To avoid the effect of immunoprophylaxis, persons born during the 36 years between 1950 and 1985, before the start of immunoprophylaxis in 1986, were examined. A mathematical model was devised to estimate the number of HBV carriers with vertical infection. It involved HBsAg positive rates stratified by sex and birth year examined in the first-time blood donors during 1995–2000 in Japan,[11] and retrieved from the fact sheet on HBV by the National Institute of Infectious Diseases.[7] HBeAg positive rates among HBsAg positive women in 10-year age groups were reported by Sasaki *et al.*[12] The efficacy of vertical infection was assumed to be 90% for carrier mothers with HBeAg and 10% for those without HBeAg.[7] Then, the number of HBV carriers with horizontal infection was obtained by subtracting the number of HBV carriers with vertical infection from the total number of HBV carriers.

There were remarkable differences between the contribution of vertical and horizontal infections to the HBV carrier rate in birth cohorts during 1950–1985 (Fig. 2). The rate of HBV carriers with vertical infection stayed constant at 0.3% through the 36 years. By contrast, the rate of carriers with horizontal infection kept decreasing through these years, from 1.43% to 0.10% in men, and from 0.95% to 0.03% in women.

Numbers of HBV carriers with vertical and horizontal infections were obtained for persons born during 1950–1985 (Table 1). However, they would not represent numbers of HBV carriers in recent years, because some of them would have been deceased. Hence, numbers of HBV carriers with vertical and horizontal infections were obtained for persons who would be alive in 2005, the year when sex- and age-specific prevalence rates of HBsAg were determined in the first-time blood donors.[20]

The estimated number of HBV carriers who were born between 1950 and 1985 and alive in 2005 is 486 038, corresponding to 93.02% of the 522 500 carriers who were born during the 36 years. Of them, the estimated number of HBV carriers with vertical infection is 185 871 and those with horizontal infection is 300 168, accounting for 38.24% and 61.76%, respectively, with a ratio of 1:1.61. Proportion of horizontal infection was greater for men than women who carried HBV (68.43% vs 51.27%, $P < 0.001$). The higher proportion of horizontal infection in men than women would be due to increased chances of body contacts during physical activities in boys than girls, resulting in the break of skin and contamination with HBsAg positive blood. In addition, immune responses to protect from persistent HBV infection might have been lower in boys than girls.

It is of a particular note that the HBV carrier rate had already decreased during 1950–1985 in Japan, before the immunoprophylaxis program was started in 1986. The decrease was due to reduction of horizontal HBV infection (Fig. 2). The diminution of horizontal HBV

infection would be due to many factors, including improved socioeconomic environments, improved awareness of risks for infection, such as sharing a toothbrush and shaver, and advanced medical maneuvers and equipment, as well as careful vaccination procedures. Disposable needles and syringes, introduced in the early 1960s and universally distributed in the late 1970s in Japan, would have given the highest impact on decreasing horizontal transmission to establish the HBV carrier state.

It may be worth mentioning that, in women, the number of horizontal transmission increased slightly during 1963–1973 (Fig. 3). This was, however, not the case for men in whom horizontal transmission decreased steadily through the study period (1950–1985). It is not certain why horizontal infection of HBV increased preferentially in women during 1963–1973. However, vertical infection increased in women also during this period. Therefore, when the ratio of vertical to horizontal transmission was compared during four timespans of approximately 10 years in the entire study period (Fig. 3), the ratio kept increasing throughout 1950–1985 in women (from 1:2.16 to 1:0.06), as in men (1:3.92 to 1:0.37).

It has to be pointed out that this study has limitations. The HBV carrier rate of pregnant mothers may have been underestimated, because HBsAg positive rates in the first-time blood donors surveyed during 1995–2000 were used to estimate it.[11] Hence, the number of HBV carriers with vertical infection might have been underestimated. Moreover, the loss of HBsAg in the natural course, which is reported in recent years,[21] might have influenced the estimation in this study toward underestimation of HBV carriers.[22,23] However, such a large-scale survey in the 1990s with the standardized HBsAg screening level throughout the entirety of Japan had not existed except in the first-time blood donors, the database used for this mathematical model. In addition in the 1990s, the questionnaires to donors before their donation had not been strict enough to exclude the high-risk group of HBV and HCV infections than in the 2000s. Therefore, it may be worthwhile to estimate the proportion of the number of HBV carriers with vertical and horizontal infections in the first-time blood donors nowadays.

These constraints notwithstanding, contribution of horizontal infection to establish HBV carrier state, in comparison with that of vertical infection, decreased remarkably over years in Japan, even before the immunoprophylaxis of babies born to HBV carrier mothers was implemented in 1986. Furthermore, the prevalence of HBsAg in children decreased sharply from 0.75% (78/10 437) in the children born during 1978–1980 to 0.04% (12/32 049) in those during 1986–1990.[24] It is to be hoped that yearly trends of horizontal and vertical transmissions to establish HBV carrier states during the post-World War II era, described herein, may help in decision-making in Japan, whether to keep resorting solely to selective vaccination, or step toward mass vaccination of babies and/or teenagers. Increasing horizontal transmission for the persistent HBV carrier state transmitted by sexual contacts, typically with a foreign subgenotype A2,[25–29] must be taken into considerations in making such decisions. For this purpose, it is imperative to estimate the number of horizontal infection with genotype A, which is expected to have accumulated rapidly, by extensive epidemiological surveys in Japan.

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APPENDIX

WE CONSTRUCTED 95% confidence intervals (CI) for the rate of hepatitis B virus (HBV) carriers with vertical infection using 95% CI for production of two positive rates. In the Appendix, we show the conduction of 95% CI for production of two positive rates. Let n_1 and n_2 be numbers of two independent groups, x_1 and x_2 be numbers of positive in each group, and $p_1 = x_1 / n_1$, $p_2 = x_2 / n_2$ be positive rates in each group. Then, the 95% CI of log p_1 and log p_2 are asymptotically normal distributed with asymptotic variance $(1 - p_1) / n_1 p_1$ and $(1 - p_2) / n_2 p_2$. Thus, 95% CI for product of two positive rates is given by $p_1 p_2 \exp\left(\pm 1.96\sqrt{(1-p_1)/n_1 p_1 + (1-p_2)/n_2 p_2}\right)$.